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The Emerging Neurobiology of Dissociative States

Relevance to PTSD

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Sensory perception often appears to be a fixed process that produces an exact transcription of the world. This view conflicts with the increasingly well-characterized distortions in perception, identity, and memory that are commonplace in everyday life (Krystal et al., 1995; Ray 1996). Generally, modest levels of stress distort perception in a manner that optimizes information processing. For example, stress may enhance the focusing of attention and the efficiency of several cognitive processes at the expense of reduced processing of peripheral stimuli in the environment. As stress becomes extreme, gross perceptual distortions emerge, including illusions and hallucinations. These perceptual alterations may occur in association with identity-related disturbances such as derealization and depersonalization. Equally profound perceptual alterations take place as people fall asleep or undergo prolonged sensory deprivation.

The term dissociation was coined by Janet (1920) to describe states where the integration of consciousness is disrupted. This concept has been employed to describe a spectrum of subjective experiences in which perceptual, affective, memory, and identity functions are altered. Particular symptoms or syndromes associated with dissociative states include distorted sensory perceptions, altered time perception, amnesia, derealization, depersonalization, conversion symptoms, fugue states, and multiple personality (Spiegel & Cardena, 1991; Bremner et al., 1992). As suggested before, dissociation may occur during traumatization (Krystal, 1968; Spiegel & Cardena, 1991; Bremner et al., 1992; Griffin et al., 1997). Clinicians have long debated whether dissociation is an adverse or adaptive consequence of traumatic stress response. Both clinical experience

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(Freud and Breuer, 1953) and laboratory data (Griffin et al., 1997) suggest that peritraumatic dissociation may reduce both the initial impact of traumatization and the degree of subsequent physiological hyperactivity. However, these studies cannot untangle the genetic and environmental factors that might have influenced the vulnerability to dissociation and the pattern of post-traumatic response (Krystal et al., 1998b).

Dissociative states and increased vulnerability to hypnotic states may also develop as ongoing sequelae of traumatization (Spiegel et al., 1988; Bremner et al., 1992). Although dissociated, acutely traumatized individuals may appear confused, emotionally dulled, or even catatonic (Kardiner, 1941; Grinker & Spiegel, 1945; Krystal, 1968). Decades following traumatization, while recalling their traumatic experiences, individuals may experience time as being slow, have altered sensory perceptions, and have feelings of unreality (Bremner et al., 1998). Less frequently, adult traumatization may produce fugue states, conversion reactions, or multiple personality as ongoing symptoms of post-traumatic stress disorder (PTSD) (Grinker & Spiegel, 1945; McDougle & Southwick, 1990).

Flashbacks, perhaps the most distinctive PTSD symptom, link dissociative, memory-related, and arousal regulatory processes pertinent to this disorder. During flashbacks, patients vividly reexperience aspects of the traumatic response while feeling detached from their surrounding environment. Ongoing sensory processing may be altered or disrupted, and patients may report that they are in a fog or that they blacked out (Bremner et al., 1993). Flashbacks involving the recollection of traumatic experiences are frequently associated with intense emotional responses and panic-like states (Mellman & Davis, 1985). Most flashbacks are brief and last only a few minutes. However, some flashbacks may last several hours or several days. Some flashbacks are accurate depictions of a traumatic situation, and others have unreal or distorted qualities, similar to dreams. Out-of-body experiences may also be associated with flashbacks (Rainey et al., 1987; Spiegel & Cardena, 1991).

Despite progress in identifying, characterizing, and quantitatively assessing dissociative states, there has been surprisingly little study of their neurobiology and few pharmacological trials specifically aimed at reducing dissociation. This chapter reviews a series of studies in PTSD patients and healthy subjects that have utilized psychopharmacological processes to evoke or suppress dissociative states in patients or perceptual alterations resembling dissociation in healthy individuals. The implications of these studies for the evaluation of novel pharmacotherapies for dissociative states in PTSD patients is considered.

Pharmacological Challenge Studies in PTSD Patients

Flashbacks have been precipitated in Vietnam veterans who have chronic PTSD by the intravenous administration of sodium lactate (Rainey et al., 1987), yohimbine (Southwick et al., 1993), and *m*-chlorophenylpiperazine (MCPP; Southwick et al., 1997). Administration of each of these substances produces panic attacks in a significant proportion of patients with either panic disorder (Pitts & McClure, 1967; Charney et al., 1984, 1987) or PTSD (Rainey et al., 1987; Southwick et al., 1993, 1997), but not in other patient groups. However, PTSD patients are the first group studied who experience flashbacks after administration of these substances.

Rainey and his associates (1987) compared the response to intravenous sodium lactate, isoproterenol, and a dextrose placebo in seven Vietnam combat veterans, six of whom also met criteria for panic disorder. All seven patients experienced flashbacks following lactate, two patients also experienced flashbacks after isoproterenol infusion, and one patient experienced a flashback during placebo infusion. The authors described these flashbacks as similar to those that occur naturally as part of PTSD. Six of the seven lactate-induced flashbacks, both isoproterenol flashbacks, and the dextrose flashback were followed by panic-like states. However, the absence of reported anxiety ratings makes it impossible to determine whether subpanic increases in anxiety preceded the flashbacks. The overlap of panic disorder and PTSD in the patients in this study was another limitation of this study because it raised concerns that lactate-induced flashbacks were a property of panic disorder and not independently associated with PTSD. Little is known about the mechanisms through which lactate produces panic attacks and flashbacks in PTSD patients.

The precipitation of flashbacks and panic attacks in PTSD patients by yohimbine, linked noradrenergic systems are implicated in fear and arousal regulation with the symptoms of PTSD (Southwick et al., 1993). Yohimbine activates central noradrenergic neurons through a blockade of alpha-2 receptors located on noradrenergic neurons. These alpha-2 receptors mediate, in part, feedback inhibition of noradrenergic neurons (Starke et al., 1975). Following yohimbine, 40% (8/20) of the patients experienced flashbacks and 70% (14/20) of the patients experienced panic attacks. No panic attacks and only one flashback emerged following placebo administration. Although 45% of the patients in this study also met DSM-III-R criteria for panic disorder, 43% of the yohimbine-induced panic attacks occurred in individuals without panic disorder. The risk of a yohimbine-induced panic attack was increased in patients with panic disorder relative to those without comorbid panic disorder (89% vs. 43%). However, a history of panic disorder did not appear to influence the likelihood of experiencing a yohimbine-induced flashback. The following vignette illustrates the features of yohimbine-induced flashback:

> 10:00 A.M.: Initiation of yohimbine infusion
> 10:05 A.M.: Subject reports hot and cold flashes, goose bumps, palpitations.
> 10:10 A.M.: Subject reports clammy hands, he asked the nurse to move away from him ... in case he felt like running. "I feel like I'm picking up dead bodies the centrifuge sounds like a helicopter .... A chopper is shooting at us, we're trying to shoot back at it! One of the guys' head is shot off! Brains are coming at me! I smell burnt flesh ... I feel scared, I can't hear what's going on ....

The operational definition for flashback employed in this study led to the exclusion of many dissociative states produced by yohimbine in the PTSD patients. The following criteria were employed to define a drug-induced flashback: (1) reexperiencing a past traumatic event during drug infusion, (2) the reexperiencing must involve one or more sensory modalities, and (3) the drug-induced state must be similar to naturally occurring flashbacks. Despite the expedient characterization of flashbacks as being present or absent, yohimbine actually produced a continuum of dissociative phenomena. Patients experienced varying degrees of derealization and depersonalization that were often accompanied by other dissociative symptoms. Yohimbine also elicited a rang of altered perceptual experiences, some of which were fragmentary or vague. For example, one patient perceived the shadow produced by a sink in the testing facility to be the

shadow made by a tank turret. In addition to stimulating flashbacks, yohimbine significantly increased the recall of traumatic memories. Although yohimbine produced symptoms of autonomic arousal in many patients, these symptoms were not the sole predictors of flashbacks within a session. Yohimbine also significantly increased the recall of traumatic memories. In some cases, symptoms of autonomic arousal followed or were coincident with the reported retrieval of traumatic memories (S. M. Southwick, personal communication). Thus, it appeared that noradrenergic systems might be involved in eliciting dissociative symptoms as a direct consequence of their central pharmacological actions on neural circuitry that contribute to dissociation and memory retrieval. These data contrasted with models in which noradrenergic contributions of PTSD symptoms were entirely mediated by peripheral autonomic systems.

A subsequent study evaluated the cortical localization of yohimbine effects in PTSD patients and in controls by studying its effects on cortical metabolism using fluorodeoxyglucose and PET (Bremner et al., 1997). This study found that yohimbine increased orbital frontal cortical metabolism in healthy subjects, perhaps by blocking the inhibitory effects of postsynaptic alpha-2 adrenergic receptors. In PTSD patients, however, yohimbine reduced orbital frontal cortex metabolism. Because locus coeruleus stimulation inhibits frontal cortical metabolism, it is possible that the finding in PTSD patients reflects enhanced norepinephrine release after yohimbine administration. This study also linked yohimbine-stimulated PTSD symptoms to modulation of the orbital frontal cortex, a brain region implicated in both emotion and cognitive functions.

One question raised by the initial yohimbine study was whether the elicitation of flashbacks by yohimbine reflected a specific response to alpha-2 receptor blockade or whether all anxiogenic drugs produce flashbacks in PTSD patients. To investigate this question, yohimbine and MCPP effects were compared in 26 PTSD patients and 14 healthy controls (Southwick et al., 1997). This study found that flashback occurred in 8 (31%) patients following yohimbine, 7 (27%) after mCPP, and 2 (8%) following placebo. Four patients (16%) had flashbacks on both the yohimbine and mCPP test days. No flashbacks occurred in control subjects. These observations do not allow one to determine whether common or distinct mechanisms mediated the drug-induced evocation of flashbacks.

Although yohimbine and mCPP produce panic attacks and flashbacks in subgroups of PTSD patients, they do not appear to have these effects when administered in comparable doses to healthy subjects. The source of the differential sensitivity of patients and healthy subjects to these medications is not yet clear. One hypothesis suggests that an adaptive reduction in alpha-2 adrenergic receptor function contributes to increased yohimbine sensitivity. This hypothesis is supported by the finding that yohimbine produced greater noradrenergic activation, as suggested by increased accumulation of the norepinephrine metabolite 3-methoxy-4-hydroxy phenethyleneglycol (MHPG) in plasma in patients with panic attacks relative to patients who did not experience panic attacks or controls (Southwick et al., 1993). To date, there is not clear evidence to support the hypothesis that alterations in the sensitivity of 5-HT receptor targets for mCPP account for the differential vulnerability to flashbacks in patients.

The vulnerability to yohimbine- and mCPP-induced flashbacks in PTSD patients may also occur as a consequence of inhibitory deficits within brain networks involving serotonin and noradrenergic systems. Deficits in endogenous opiate systems may have contributed to the PTSD-related vulnerability to yohimbine-evoked flashbacks. Opiate antagonist-induced withdrawal has stimulated flashbacks in opiate-dependent PTSD

patients (Kosten & Krystal, 1988). The association between endogenous opiate systems and noradrenergic systems is also suggested by the potentiation of the panicogenic and MHPG-increasing effects of yohimbine by naloxone in healthy subjects (Charney et al., 1986). Although this study did not directly measure dissociative states, yohimbine-precipitated panic has been previously linked to symptoms including derealization and depersonalization (Krystal et al., 1988).

Deficits in gamma aminobutyric acid-A (GABA-A) receptor function may also contribute to a vulnerability to mCPP-induced dissociation. In a clinical laboratory-based model, deficits in GABA function may be produced by the benzodiazepine partial inverse agonist, iomazenil. This drug created a vulnerability to mild dissociation-like perceptual changes in healthy subjects administered mCPP (Gil et al., 1996). Alterations in GABA function have been studied in PTSD patients. The failure of the benzodiazepine antagonist, flumazenil, to produce flashbacks in PTSD patients suggests that this disorder is not associated with significant constriction of their field of attention that results in the sensation of tunnel vision or the feeling that they were surrounded by fog. Ketamine also produced learning and memory impairments. Its effects increased proportionately to the dose administered and the duration of delay between stimulus presentation and testing. In addition, ketamine interfered with executive functions, such as abstraction, assessed by proverb interpretation, and problem solving, evaluated by the Wisconsin Card Sorting Test. Ketamine also produced emotional responses. At low doses, it had mild anxiolytic properties, whereas larger doses produced euphoria and anxiety. Anxiety stimulated by ketamine appeared to follow perceptual alterations and thought disorganization and to be related to their degree of comfort with ketamine effects on perception and thought processes.

To date, a series of studies has attempted to block the perceptual alterations produced by ketamine (summarized in Table 1). Several studies conducted in the anesthesiology field suggested that lorazepam reduced the perceptual effects of ketamine, particularly at high lorazepam doses. To evaluate this possibility, the effects of lorazepam pretreatment upon ketamine response was studied. Lorazepam (2 mg) administered orally two hours before ketamine administration tended to reduce altered environmental perceptions produced by ketamine. However, it had no effects on other dissociative symptoms or psychotic states produced by ketamine (Krystal et al., 1998a).

TABLE 1. Pharmacological Modulation of Perceptual Changes Resembling Dissociation Produced by the NMDA Antagonist, Ketamine, in Healthy Subjects[a]

Pretreatment	Degree of reduction[b]	*N*
Lorazepam, 2 mg, p.o.	+	23
Haloperidol, 5 mg, p.o.	0	20
Clozapine, 25 mg, p.o.	0	8
Glycine, 0.1 or 0.2 g/kg, i.v.		7
Lamotrigine, 300 mg, p.o.	++	10

[a]Krystal et al., 1999; Krystal et al 1998a; Lipschitz et al., 1997; D'Souza et al., 1997; Anand et al., 1997.
[b]Degree of reduction: 0 = no change to ++ = significant reduction.

Haloperidol (5 mg) and clozapine (25 mg) failed to reduce dissociative symptoms or amnesic effects produced by ketamine (Krystal et al., 1998a; Lipschitz et al., 1997). These data are consistent with the literature suggesting that neuroleptics have limited efficacy in treating dissociative symptoms (Kluft, 1987). Haloperidol reduced other ketamine-induced cognitive impairments, such as concrete ideation or poor performance on the Wisconsin Card Sorting Test (Krystal et al., 1999b).

To date, there have not been formal evaluations of ketamine effects in PTSD patients or patients with other dissociative disorders. However, anecdotal data from Russian studies suggest that ketamine induces dissociative states and may promote guided recollection of traumatic material in Russian-Afghanistan war veterans with PTSD (E. Krupitsky, personal communication).

Dissociative states have also been produced by psychoactive cannabinoids, such as tetrahydrocannabinol, the principal psychoactive component of marijuana and hashish. Cannabinoids bind to a specific G-protein-coupled receptor (Herkenham et al., 1990) through which they alter cellular functions, including blockade of N-type calcium channels, inhibition of cyclic AMP accumulation, and stimulation of arachidonic acid and intracellular calcium release (Felder et al., 1993). Some cannabinoid effects may be mediated by stimulation of glucocorticoid receptors (Eldridge & Landfield, 1990) and blockade of N-methyl-D-aspartate receptors (Feigenbaum et al., 1989). At high doses, cannabinoid intoxication produces depersonalization, derealization, temporal disorientation, perceptual alterations, and insight impairments (Melges et al., 1970; Dittrich et al., 1973). Depersonalization and temporal disorientation produced by marijuana smoking were associated with increased cortical regional cerebral blood flow assessed with the ^{133}xenon inhalation technique (Mathew et al., 1992). Cannabis has been reported to produce flashbacks in the drug-free state that resemble cannabis intoxication (Hollister, 1986). In one study (Stanton et al., 1976), 3% (1/31) of habitual marijuana users and 1% (3/348) of nonhabitual users reported flashbacks when drug-free, suggesting that flashbacks were not a frequent consequence of cannabis use. However, this study suggested that marijuana use also enhanced the likelihood of experiencing flashbacks following ingestion of serotonergic hallucinogens.

Serotonergic hallucinogens, such as lysergic acid diethylamide (LSD), mescaline, and dimethyltryptamine (DMT), also produce dissociative symptoms. These agents stimulate serotonin-2 (5-HT_2) receptors (Rasmussen et al., 1986). Serotonergic hallucinogens produce pronounced visual hallucinations, illusions, synesthesia, and expansive or portentous emotional responses (Freedman, 1968; Strassman et al., 1994). Following ingestion of psychedelics, feelings of derealization or depersonalization are prominent. Environmental stimuli may be experienced in a fragmented manner, body image distortion is common, and feelings of emotional detachment may arise (Savage, 1955; Freedman, 1968). Some clinicians have also reported that LSD may facilitate the recall of repressed memories (Freedman, 1968), although this capacity has never been rigorously evaluated. Relative to the phencyclidine or ketamine experience, psychedelic hallucinogens tend to produce perceptual effects that predominate over dissociative effects and impairments in higher cognitive functions (Rosenbaum et al., 1959).

Flashbacks have been reported in healthy individuals following serotonergic hallucinogen use. Freedman (1968) and Horowitz et al. (1969) suggested that LSD intoxication was traumatic for some users because it diminished control over awareness, resulting in intense emotional states experienced as beyond their control. In such cases, LSD flashbacks might have a traumatic etiology. However, some LSD-like experiences,

such as synesthesia, may be reexperienced long after drug ingestion by individuals who find such experiences pleasant. These effects do not easily fit a trauma model, suggesting that sensitization, conditioning, or state-dependent learning might also apply (Freedman, 1968, 1984; Horowitz et al., 1969; McGee, 1984). Subject expectancy may also play a role in drug-like flashbacks. One study found that flashbacks may be produced in healthy subjects following placebo administration, if subjects are coached to anticipate that a placebo will produce flashbacks (Heaton, 1975). Heaton suggested that the expectancy of flashbacks led subjects to mislabel and selectively attend to aspects of normal experience that are consistent with a flashback-like experience.

Synthesis and Clinical Implications

The studies reviewed in this chapter chart the slow but steady progress made in characterizing the psychopharmacology of dissociative states in PTSD patients and dissociation-like perceptual changes in healthy individuals. The studies reviewed in this chapter suggest that one fundamental insight into the neurobiology of dissociation may come from the observation that some drugs given at specific doses produce dissociative symptoms in traumatized individuals, but not in healthy controls. Yohimbine and mCPP fit into this class. Other drugs, such as ketamine, cannabis, and hallucinogens, produce dissociation-like responses in individuals without histories of traumatization or dissociative disorders.

Dissociative States and the Activation of Cortical Glutamatergic Neurons

The significance of these distinctions is not yet clear but may be linked to the intrinsic organization of the cerebral cortex or the pharmacology of cortical function, as illustrated in Figure 1 (reviewed in Lewis, 1992; Krystal et al., 1999a). The cerebral cortex contains both pyramidal and nonpyramidal neurons. Pyramidal neurons release excitatory amino acids, primarily glutamate. Cortical pyramidal neurons are primarily responsible for cortico–cortical and cortico–subcortical communication. The nonpyramidal neurons predominantly release GABA and inhibit the activity of pyramidal neurons. One class of GABAergic interneurons is the chandelier cells. These cells provide feedback inhibition to cortical pyramidal neurons. Cortical pyramidal neurons and interneurons receive innervation from noradrenergic, serotonergic, and opiatergic neurons. These monoamine and peptide systems provide important modulation of the release of both amino acid neurotransmitters.

Stress has important modulatory effects on the release of many neurotransmitters, including monoamines, endogenous opiates, GABA, and serotonin (Charney et al., 1993). More recently, research has begun to characterize stresss-related stimulation of cortical glutamate release in the prefrontal cortex (Moghaddam, 1993). A series of studies suggested that stress-related glutamate release in conjunction with parallel enhancements in the levels of circulating glucocorticoids promoted the death of hippocampal neurons in the CA3 region of the hippocampus (Sapolsky, 1992). However, the release of glutamate may have important implications in evoking stress-related perceptual changes.

Some insights into the importance of alterations in cortical glutamate function for dissociation may be derived from studies of NMDA antagonists, including ketamine.

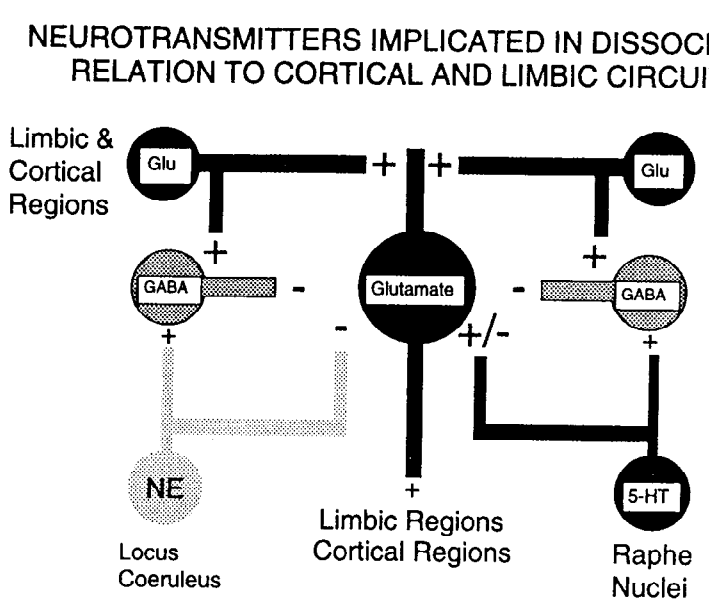

FIGURE 1. This figure provides a schematic representation of interactions that are predicted to contribute to dissociative states on the basis of human psychopharmacological studies and preclinical studies reviewed in the text. This schematic depicts the convergence of cortical GABAergic and glutamatergic inputs on a prototypical glutamatergic pyramidal neuron. This neuron, in turn, provides glutamatergic input to both cortical and limbic regions. Extrinsic inputs to the cortex from the noradrenergic locus coeruleus and serotonergic raphe nuclei appear to modulate the activity of intrinsic cortical populations. Activation of these inputs or direct stimulation or blockade of postsynaptic receptors, as reviewed in the text, appears to precipitate dissociative symptoms in vulnerable traumatized patients. In contrast, blockade of NMDA receptors by ketamine or stimulation of 5-HT_2A receptors by serotonergic hallucinogens appears to activate glutamatergic activity and to evoke dissociation-like perceptual changes in healthy subjects. Abbreviations: Glu: glutamate-containing; NE: norepinephrine-containing; 5-HT: serotonergic. All other abbreviations are defined in the text.

Components of ketamine response may mimic the impact of stress upon glutamate release. For example, ketamine and other NMDA antagonists increase the release of glutamate within the frontal cortex (Moghaddam et al., 1997). Although the mechanism underlying the glutamate-releasing effect of NMDA antagonists is not fully clear, some preclinical research suggests that these drugs may inhibit the activity of chandelier cells in the cortex or GABAergic cells that play similar roles in the hippocampus (see Krystal et al., in press c). Glutamate that is released during NMDA antagonist administration primarily stimulates non-NMDA receptors (AMPA/kainate and metabotropic glutamate receptors) because the NMDA receptors are blocked by the antagonist (Figure 2). Thus, NMDA antagonists effects might reflect the direct postsynaptic effects of NMDA receptor blockade, the excessive stimulation of non-NMDA glutamate receptors, and possibly shifts in the relative degree of stimulation of NMDA and non-NMDA receptors.

Recent clinical data support the hypothesis that cognitive and perceptual changes produced by NMDA antagonists reflect a hyperglutamatergic state combined with a deficit in NMDA receptor function. Consistent with the preclinical literature, ketamine increases cortical metabolism, as assessed by the FDG-PET technique (Breier et al., 1997). Further, two ongoing studies suggest that the effects of ketamine on perception may be reduced by enhancing NMDA receptor function or by reducing ketamine-

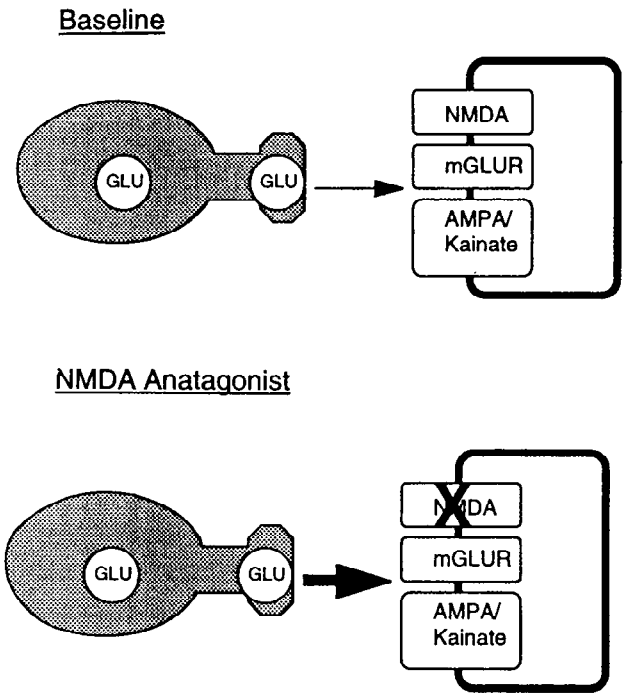

FIGURE 2. This figure depicts the impact of ketamine and other NMDA antagonists upon glutamate neuronal activity. The neuronal release of glutamate stimulates postsynaptic NMDA, AMPA, kainate, and metabotropic glutamate receptors. NMDA antagonists, such as ketamine, active glutamate neuronal activity causing increased stimulation of non-NMDA receptors. Abbreviations not defined in the text: GLU: glutamate; AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid.

stimulating glutamate release. The first of these studies evaluated the effects of large intravenous glycine doses on ketamine response (D'Souza et al., 1997). Glycine binds to a strychnine-insensitive site on the NMDA receptor complex where it acts as a coagonist (D'Souza et al., 1995). In the initial seven patients studied, both glycine 0.1 g/kg and glycine 0.2 g/kg reduced CADSS (Clinician-Administered Dissociative States Scale) scores in healthy subjects administered ketamine. Another study evaluated the effects of lamotrigine pretreatment upon ketamine response. Lamotrigine reduces glutamate release through several mechanisms, including blockade of sodium channels and antagonism of N-type calcium channels (Rataud et al., 1994; Wang et al., 1996).

Cortical Networks, Dissociation, and PTSD

As suggested by Figure 1, one consequence of activation of cortical glutamate neurone by stress, ketamine, or 5-HT_2A receptors is enhancing glutamate release within key limbic and cortical projection areas. Ketamine, for example, has activated frontal cortex and cingulate gyrus metabolism and blood flow in healthy humans and schizophrenic patients (Breier et al., 1997; Lahti et al., 1995). NMDA antagonists have also shown evidence of activating a cortical network involving the striatum, globus pallidus, subthalamic nucleus, and thalamus (Carlsson and Carlsson, 1990). Recent neuroimaging studies have suggested that the cingulate gyrus and thalamus may be activated in PTSD patients by exposure to reminder s of their traumas (Rausch et al., 1996; Liberzon

et al., 1996/1997). In contrast, the orbital frontal gyrus may be inhibited during worsening of PTSD symptoms produced by reminders of the trauma or yohimbine (Rausch et al., 1996; Bremner et al., 1997). The involvement of the thalamus and cingulate gyrus in evoking PTSD is interesting in the light of other data implicating these regions in the control of attention and sensory processing (Krystal et al., 1995). The overlap among the neuroimaging studies reviewed in this paragraph raise the possibility that cortico–striato–thalamic circuitry modulated by ketamine also contributes to evoking the reexperiencing cluster of PTSD symptoms, including flashbacks.

Therapeutic Implications

The introduction of benzodiazepines and antidepressants into the pharmacotherapeutic armamentarium advanced the treatment of post-traumatic stress disorder significantly (Friedman and Southwick, 1995). The efficacy of these medications in treating PTSD is quite consistent with the yohimbine and mCPP testing performed in PTSD patients. Thus, the efficacies of benzodiazepines and antidepressants are consistent with the view that activation of monamine is intimately involved in the interplay of neurobiological processes that give rise to PTSD symptoms, including dissociation. Further, the impact of monoaminergic activation may be reduced by facilitation of GABA-A receptor function (reviewed in Gil et al., 1996). However, several promising treatments based on preclinical models have remained peripheral in treating PTSD. For example, clonidine and propranolol were evaluated in PTSD to prevent or reduce the consequences of central noradrenergic systems based on promising clinical and preclinical evidence that implicated central noradrenergic systems in the symptoms of PTSD (Kolb et al., 1984). The anticonvulsants carbamazepine and valproic acid were evaluated in PTSD based on the hypothesis that repeated exposure to stress sensitizes or "kindles" cortical networks (Lipper et al., 1986). Similarly, naltrexone was evaluated in PTSD based on the hypothesis that traumatic stress and subsequent stressful experience causes a rewarding release of endogenous opiates (Friedman and Southwick, 1995). Despite their limited use in treating PTSD, the precise role of each of these novel treatments remains to be precisely characterized. Generally, the pharmacotherapeutic approaches to PTSD referred to in this paragraph are now more than 10 years old. Given the limited, but important, efficacy of these approaches, it appears that there is a need for novel approaches to the neurobiology of clusters of PTSD symptoms to drive the next generation of medication development for this disorder.

The central question of this chapter is whether the effects of NMDA antagonists in healthy humans have pharmacotherapeutic implications for dissociative symptoms in PTSD patients or patients with other dissociative disorders. It may be that the perceptual effects of ketamine do not provide an accurate model for dissociative symptoms associated with PTSD or other dissociative disorders beyond the level of phenomenological similarity. Bearing this concern in mind, one might attempt to build on a glutamatergic model by testing the efficacy of drugs that block the perceptual effects of ketamine in humans. Based on this criterion, one would endorse the efficacy of benzodiazepines and the relative lack of efficacy of neuroleptics in PTSD. This laboratory-based model also suggests two novel pharmacological approaches to the treatment of PTSD: (1) agonists of the strychnine-insensitive glycine site of the NMDA receptor complex and (2) drugs, such as lamotrigine, that reduce ketamine effects on glutamate release. One might also evaluate drugs that block the postsynaptic consequences of enhanced

glutamate release by studying the effects of antagonists of non-NMDA glutamate receptors. The caveat here, though, is that a subclass of metabotropic glutamate receptors inhibit glutamate, the mGLUR II/III receptors (Schoepp and Conn, 1993). Agonists, rather than antagonists of these receptors would be predicted to be helpful in PTSD.

Implications

This chapter continues a line of discourse that began almost 15 years ago (van der Kolk et al., 1985) that attempts to integrate animal research and human laboratory-based paradigms in developing models for the neurobiology and pharmacotherapy of PTSD. The utility of these models is ultimately determined by the definitive evaluation of the effectiveness of rationally developed pharmacotherapies. In advance of the clinical data, the laboratory-based paradigms continue to be a source of creative approaches to the pathophysiology and pharmacotherapy of PTSD.

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